In the Specification:

Please replace the current title with the following, "~~MULTI-ARMED, MONOFUNCTIONAL, AND HYDROLYTICALLY STABLE DERIVATIVES OF POLY)ETHYLENE GLYCOL) AND RELATED~~ PURIFIED POLYMERS FOR MODIFICATION OF SURFACES AND MOLECULES"

Please amend the paragraph on page 1, lines 1 through 6 as follows:

This application is a continuation of U.S. Patent Application Serial No. 10/119,546, filed April 10, 2002; which is a continuation of U.S. Patent Application Serial No. 09/939,867, filed August 27, 2001, now abandoned; which is a continuation of U.S. Patent Application Serial No. 09/140,907, filed August 27, 1998, now abandoned; which is a continuation of U.S. Patent Application Serial No. 08/443,383, filed May 17, 1995, now U.S. Patent No. 5,932,462; which is a continuation-in-part of U.S. Patent Application Serial No. ~~related to and claims the benefit of the filing date of USSN~~ 08/371,065, ~~which was~~ filed on January 10, 1995, now abandoned. ~~and is entitled MULTI-ARMED, MONOFUNCTIONAL, AND HYDROLYTICALLY STABLE DERIVATIVES OF POLY(ETHYLENE GLYCOL) AND RELATED POLYMERS FOR MODIFICATION OF SURFACES AND MOLECULES~~.

Please amend the last paragraph on page 2, beginning on line 32, through page 3, line 9, as follows:

However, despite the benefits of modifying polypeptides with polymer derivatives, additional problems have arisen. These problems typically arise in the linkage of the polymer to the polypeptide. The linkage may be difficult to form. Bifunctional or multifunctional polymer derivatives tend to ~~cross link~~ cross-link proteins, which can result in a loss of solubility in water, making a polymer-modified protein unsuitable for circulating through the ~~blood stream~~ bloodstream of a living organism. Other polymer derivatives form hydrolytically unstable linkages that are quickly destroyed on injection into the ~~blood stream~~

bloodstream. Some linking moieties are toxic. Some linkages reduce the activity of the protein or enzyme, thereby rendering the protein or enzyme less effective.

Please amend the second full paragraph on page 7, beginning on line 14, to read as follows:

Proteins and other molecules typically have a limited number and distinct type of reactive sites available for coupling, such as the epsilon $-NH_2$ moiety of the lysine fraction of a protein. Some of these reactive sites may be responsible for a protein's biological activity. A PEG derivative that is attached to a sufficient number of such sites to impart the desired characteristics can adversely affect the activity of the protein, which offsets many of the advantages otherwise to be gained.

Please amend the first full paragraph on page 8, beginning on line 7, to read as follows:

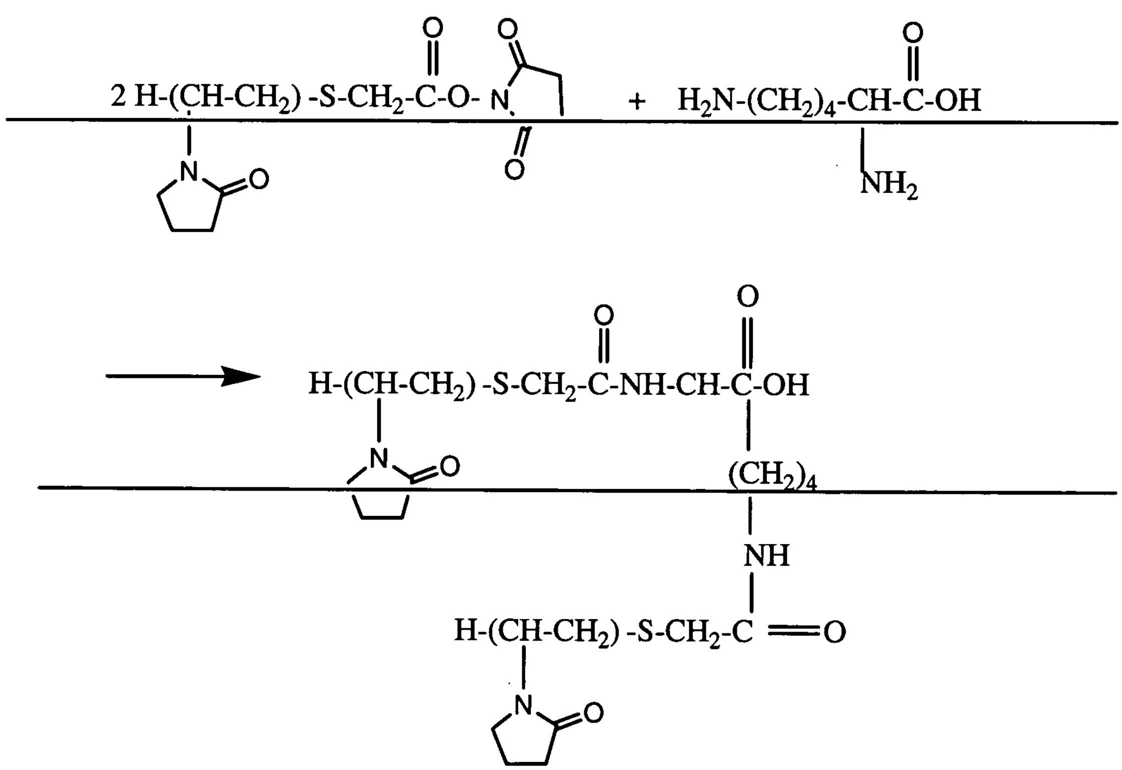
These monofunctional mPEG polymer derivatives show a branched structure when linked to another compound. One such branched form of mPEG with a single active binding site, -Z, has been prepared by substitution of two of the ~~chloride~~ chlorine atoms of trichloro-s-triazine with mPEG to make mPEG-disubstituted chlorotriazine. The third chloride is used to bind to protein. An mPEG disubstituted chlorotriazine and its synthesis are disclosed in Wada, H., Imamura, l., Sako, M., Katagiri, S., Tarui, S., Nishimura, H., and Inada, Y. (1990) Antitumor enzymes: polyethylene glycol-modified asparaginase. *Ann. N.Y. Acad. Sci.* 613, 95-108. Synthesis of mPEG disubstituted chlorotriazine is represented structurally below.

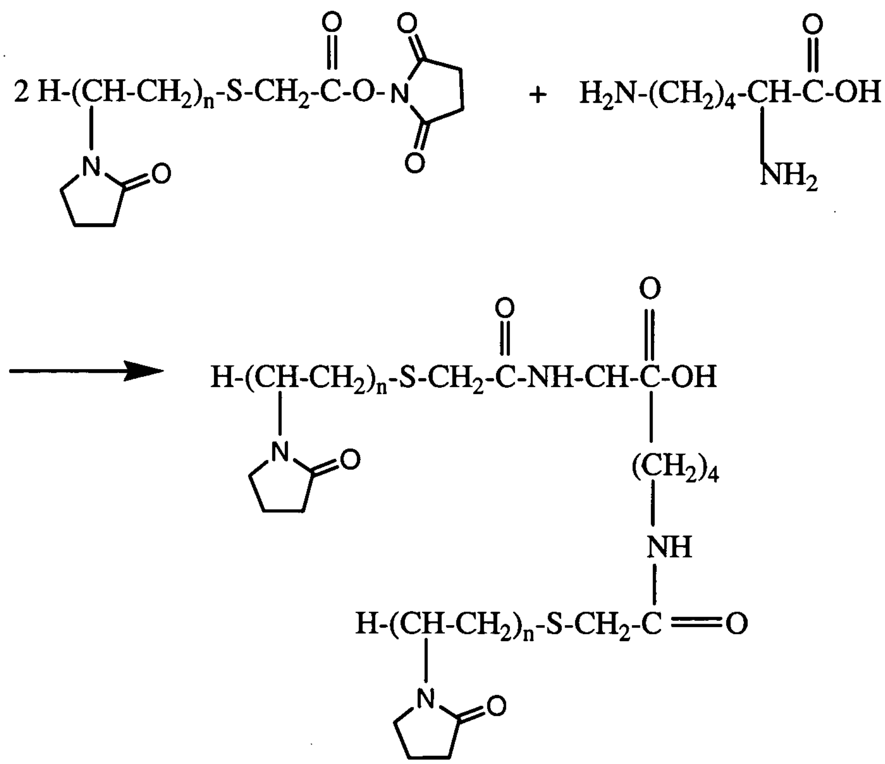
Please amend the second full paragraph on page 11, beginning on line 16, to read as follows:

The invention provides a branched or "multi-armed" amphiphilic polymer derivative that is monofunctional, hydrolytically stable, can be prepared in a simple, one-step reaction, and possesses no aromatic moieties in the linker fragments forming the linkages with the polymer

moieties. The derivative can be prepared without any toxic linkage or potentially toxic fragments. Relatively pure polymer molecules of high molecular weight can be created. The polymer can be purified by ~~chromotography~~ chromatography in water. A multi-step method can be used if it is desired to have polymer arms that differ in molecular weight. The polymer arms are capped with relatively nonreactive end groups. The derivative can include a single reactive site that is located along the polymer backbone rather than on the terminal portions of the polymer moieties. The reactive site can be activated for selective reactions.

On page 49, please delete the following reaction scheme beginning on line 6, and replace it with the underlined scheme shown below:





Please amend the second paragraph on page 51, beginning on line 11, to read as follows:

Six and two tenths grams of mPEG- disubstituted lysine of molecular weight 10,000, which is about 0.6 millimoles, was dissolved in 10 milliliters of anhydrous methylene chloride and cooled to 0°C. N-hydroxysuccinimide and N,N-dicyclohexylcarbodiimide ("DCC") were added under stirring in the amounts, respectively, of 0.138 milligrams, which is about 1.2 millimoles, and 0.48 milligrams, which is about 1.2 millimoles. The reaction mixture was stirred overnight at room temperature. Precipitated dicyclohexylurea was removed by filtration and the solution was concentrated and precipitated with diethyl ether. The product, mPEG disubstituted lysine activated as the ~~succinimidyal~~ succinimidyl ester, was crystallized from ethyl acetate. The yield of esterification, calculated on the basis of hydroxysuccinimide absorption at 260 nm (produced by hydrolysis), was over 97% (ε of hydroxysuccinimide at 260 nm = 8,000 $m^{-1}cm^{-1}$).

The NMR spectrum was identical to that of the unactivated carboxylic acid except for the new succinimide singlet at 2.80 ppm (2Hs)

Please amend the first full paragraph on page 52, beginning on line 3, to read as follows:

The procedure previously described for the activation of the mPEG-disubstituted lysine of molecular weight 10,000 was also followed for the activation of the higher molecular weight polymer of molecular weight approximately 40,000 that was produced in accordance with the one step procedure discussed above. The yield was over 95% of high molecular weight mPEG-disubstituted lysine activated as the ~~succinimidyal~~ succinimidyl ester.

Please amend the second full paragraph on page 52, beginning on line 12, to read as follows:

It should be recognized that a number of activating groups can be used to activate the multisubstituted polymer derivatives for attachment to surfaces and molecules. Any of the activating groups of the known derivatives of PEG can be applied to the multisubstituted structure. For example, the mPEG-disubstituted lysine of the invention was functionalized by activation as the succinimidyl ester, which can be attached to protein amino groups. However, there are a wide variety of functional moieties available for activation of ~~carboxylic~~ carboxylic acid polymer moieties for attachment to various surfaces and molecules. Examples of active moieties used for biological and biotechnical applications include trifluoroethylsulfonate, isocyanate, ~~isosthiocyanate~~ isothiocyanate, active esters, active carbonates, various aldehydes, various sulfones, including chloroethylsulfone and vinylsulfone, maleimide, iodoacetamide, and iminoesters. Active esters include N-hydroxylsuccinimidyl ester. Active carbonates include N-hydroxylsuccinimidyl carbonate, *p*-nitrophenylcarbonate, and trichlorophenylcarbonate.

Please amend the reaction scheme on page 55, beginning at line 21 to appear as follows: